binding domain (MPBD) does not reasonably provide enablement for a method employing any kind of modular protein binding domain".

It is noted that the instant application was filed on March 24, 2001 and claims the priority of a PCT application dated June 29, 2000 and a Provisional Application dated June 30, 1999. The application therefore was copending with the Michnick patent (6,270,964 B1) which issued August 7, 2001. While this patent can be cited as prior art (35 U.S.C. 102(e)) by the Examiner, the Michnick publication referred to by the applicant in the specification for example at pages 5 and 9 while dated before the application's filing date is dated after the two documents as to which priority is claimed. Michnick (J.Mol. Biol. 295 : 627-639 (2000) was known to the applicant and while directed to subject matter as to which the instant invention is patentably distinct discloses (constitutes disclosure) "that the high affinity coiled-coil heterodimerization domains of the present invention are the WIN-ZIP coiled-coil heterodimerization leucine zippers, such as those described by Michnick and colleagues (See, e.g., Arndt, K.M., J.N.Pelletier, K.M. Muller, T. Alber, S.W. Michnick and A. Pluckthun, A heterodimeric coiled-coil peptide pair selected in vivo from a designed library-versus-library ensemble, *J. Mol. Biol.* **295**: 627 - 630 (2000) pages 4-5 of specification" and at page 9, that in "a preferred embodiment of the present invention, a coiled-coil dimerization system based on the WIN-ZIP synthetic zippers first described by Michnick and colleagues are employed (See, Arndt, K.M., J.N. Pelletier, K.M. Muller, T. Alber, S.W. Michnick, and A. Pluckthun. A heterodimeric coiled-coil peptide pair selected in vivo form a designed library-versus-library ensemble, *J. Mol. Biol.* **295**: 627 - 639 (2000). These zippers have been found by the present inventor to work in cells at an affinity comparable to those of biologically important interactions". As will be pointed out, these materials were known and available at the time the instant invention was conceived and first reduced to practice and constitute knowledge not only to the inventor but to others skilled in this art.

The same is true of certain of the prior art which has been provided in the Information Disclosure Statement filed by the applicant. The prior art was available to be relied on by the skilled in the art and in many instances to assist him or her in practicing the techniques, etc., disclosed without having to resort to undue experimentation.

The applicant's invention is fundamentally different from the cited Michnick patent and publication in objective and realization but it incorporates certain teachings of the prior art and can be relied on for the purpose of disclosure as it represents the state of the art as to enablement.

The Michnick patent is directed to an assay and a method for implementing the same and is identified as the protein-fragment complementation assay (or PCA) and discloses various uses thereof. In the PCA, an enzyme or other protein that has an assayable activity is split into two inactive halves and when the two halves are brought [back] together in the cell or in vitro, for example when each inactive half is fused to a protein interaction domain, and the two protein interaction domains can bind to each other then enzymatic or other activity is restored and can be detected. This has many uses, for example identifying a protein or fragment that can bind to another protein or fragment, or assaying where and when two proteins interact in the cell. Fundamentally, it is a way to detect and quantify the interaction of two separate protein species whose ability to interact with each other is previously unknown or uncharacterized.

In contrast, in accordance with the invention, functional interaction trap (FIT), a defined protein interaction domain is utilized ZIP A and ZIP B , which bind to each other to address what the consequences of interaction of two proteins such as an enzyme and its substrate might be. ZIP A is fused to one protein, and ZIP B is fused to a second protein, both are expressed in the cell and the output, for example, the cellular consequence of the phosphorylation of the second protein is analyzed.

This is almost precisely a mirror image of what the Michnick PCA assay is designed to do. In the PCA assay, the output is fixed by quantitating the activity of the enzyme when the two halves are brought together and the assay measures whether or not the two inactive halves interact in a way that restores full or partial enzymatic activity. In the FIT assay, on the other hand, the protein interaction is fixed by ZIP A and ZIP B, and the assay tests for what the consequences of that interaction might be - the consequences of the interaction of the proteins fused to ZIP A and ZIP B, respectively and not the consequences of the interaction of ZIP A with ZIP B.

In spite of these entirely different and distinct mechanism, protein and protein fragments ZIP A and ZIP B etc. are overlapping and these are known by virtue of their having been described in publications available to the art.

The skilled in the art would have no difficulty in practicing the invention, i.e., they would find the applicant's disclosure taken with the teachings of the art to be readily enabling.

A patent speaks to a person of ordinary skill in the art, not the general public. The question is whether the disclosure is sufficient to enable one skilled in the art to practice the claimed invention. It is not necessary to explain every detail, since the inventor is speaking to persons of ordinary skill DeGeorge v. Bernier, 768 F.2d 1318, 226 U.S.P.Q. 758 (Fed. Cir. 1985).

A patent need not teach, and preferably omits, what is well known in the art. Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986). See also Paperless Accounting, Inc. v. Bay Area Rapid Transit Sys., 804 F.2d 659, 231 U.S.P.Q. 649 (Fed. Cir. 1986). Nonetheless, practice of the invention must not require undue experimentation. What is "undue" defies precise definition. That some experimentation is necessary does not preclude enablement Lindemann Maschinenfabrik v. American Hoist & Derrick Co., 730 F.2d 1452, 221 U.S.P.Q. 481(Fed. Cir. 1984). See also Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986), but it is clear that any required experimentation must be reasonable. Some trial and error is permissible. Indeed, it may be sufficient if enablement of use is obvious from the prior art. White Consol. Indus., Inc. v. Vega Servo-Control, Inc., 713 F.2d 788, 218 U.S.P.Q. 961 (Fed. Cir. 1983).

The Examiner has also rejected claims 28 and 29 under 35 U.S.C. 112, second paragraph as being indefinite. The newly added claims are believed to render moot this rejection. New claim 30 is a generic claim and new claim 32 corresponds to the elected species. The word "looking" has been deleted and detecting and measuring substituted therefor. The language of the new claim corresponds to the language found at page 5 of the application.

The Examiner has rejected claims 28 and 29 as being anticipated (35 U.S.C. 102) or in the alternative obvious (35 U.S.C. 103) over Michnick (6,270,964) or applicant's disclosure of known prior art (p. 9 lines 12-17 of the application).

It has been pointed out above that Michnick was included in the application to provide disclosure. First at pages 4-5, the applicant summarizes his invention as the discovery that novel fusion proteins having high affinity coiled-coil heterodimerization domains (Kd of heterodimerization interaction less than, or equal to, 30nM, more preferably less than, or equal to, 28 nM, and more preferably less than, or equal to, 26 nM) in place of a modular protein binding domain can be used in assays to identify the effect of protein-protein interactions and continues that the "particularly preferred high affinity coiled-coil heterodimerization domains of the present invention are the WIN-ZIP coiled-coil heterodimerization leucine zippers, such as those described by Michnick and colleagues (See, e.g., Arndt, K.M., J.N.Pelletier, K.M. Muller, T. Alber, S.W. Michnick and A. Pluckthun, A heterodimeric coiled-coil peptide pair selected in vivo from a designed library-versus-library ensemble, *J. Mol. Biol.* **295**: 627 - 630 (2000).

At pages 7-9, the applicant describes his invention in greater detail and recites the FIT assay of the present invention depends on a protein binding interface consisting of two engineered protein segments, coiled-coil heterodimerization segments, each fused in-frame to one of two proteins. Only when both modified proteins are expressed in the same cell will the two proteins bind each other, and the unique biological consequences of the interaction be assessed. Since the fusion proteins of the present invention act positively, namely by actually interacting, one can look for generation of a function instead of loss of function for the complex. In this connection to provide disclosure, Michnick is referenced and specifically high affinity coiled-coil heterodimerization domains of the present invention are the WIN-ZIP coiled-coil heterodimerization leucine zippers, such as those described by Michnick and colleagues (See, e.g., Arndt, K.M., J.N.Pelletier, K.M. Muller, T. Alber, S.W. Michnick and A. Pluckthun, A heterodimeric coiled-coil peptide pair selected in vivo from a designed library-versus-library ensemble, *J. Mol. Biol.* **295**: 627 - 630 (2000).

The applicant has said I employ certain known subject matter but in an entirely different scheme to accomplish entirely different ends.

Michnick has used his assay (PCA) to teach the consequences of the interaction of the proteins fused to ZIP A and ZIP B respectively and not the consequences of the interaction of ZIP A with B, i.e., the uses ZIP A and ZIP B as a component of a completely new assay for the functional consequences of protein interaction.

This is not the same nor is it obvious from Michnick.

The Michnick patent is directed to determining whether specific pairs of proteins and peptides interact with each other. The focus is on the "protein interaction domains" of the proteins/peptides of interest. The Michnick approach is such that a protein's activity (such as enzymatic activity) is restored and can be measured only when the proteins of interest interact with each other. The enzymatic activity of the restored protein is the only possible type of "read-out" of the assay.

The instant invention uses proteins with known interaction characteristics (such as the coiled coil interaction of Win-zip A and Win-zip B) to bring together in a controlled manner a catalytic (enzymatic) protein, such as a kinase, with another protein, such as a biologically important target substrate (or a potential substrate) of the kinase. The invention is conducted in cells and the realized result is a detectable change in the characteristics of the cell, such as motility, morphology, growth rate, etc. This allows the study of the biological consequences of a protein modification such as for example, phosphorylation.

For at least all of the reasons above set forth the invention is not anticipated or obvious from Michnick.

It is submitted that the claim drawn to an assay with a fusion containing the elected species, SH_3, is allowable to the applicant (the Examiner has stated such a claim is free of the prior art) and that the same is true of the generic claim(s) and notification to this effect is respectfully requested.

Any additional fees required for the addition of new claims should be charged to the account of the undersigned No. 11-0231.

Respectfully submitted,

Evelyn M. Sommer, Reg. No. 19,603
Cummings & Lockwood
700 State Street
P. O. Box 1960
New Haven, CT 06509-1960
Tele: (203) 351-4229
Fax: (203) 359-4535

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